Diagnostic Imaging Pathways - First Trimester Screening

Population Covered By The Guidance

This pathway provides guidance on the screening of pregnant women to detect fetal abnormalities in early pregnancy.

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Quick User Guide

Move the mouse cursor over the PINK text boxes inside the flow chart to bring up a pop up box with salient points.
Clicking on the PINK text box will bring up the full text.
The relative radiation level (RRL) of each imaging investigation is displayed in the pop up box.

SYMBOL	RRL	EFFECTIVE DOSE RANGE
	None	0
	Minimal	< 1 millisieverts
	Low	1-5 mSv
	Medium	5-10 mSv
	High	>10 mSv

Pathway Diagram

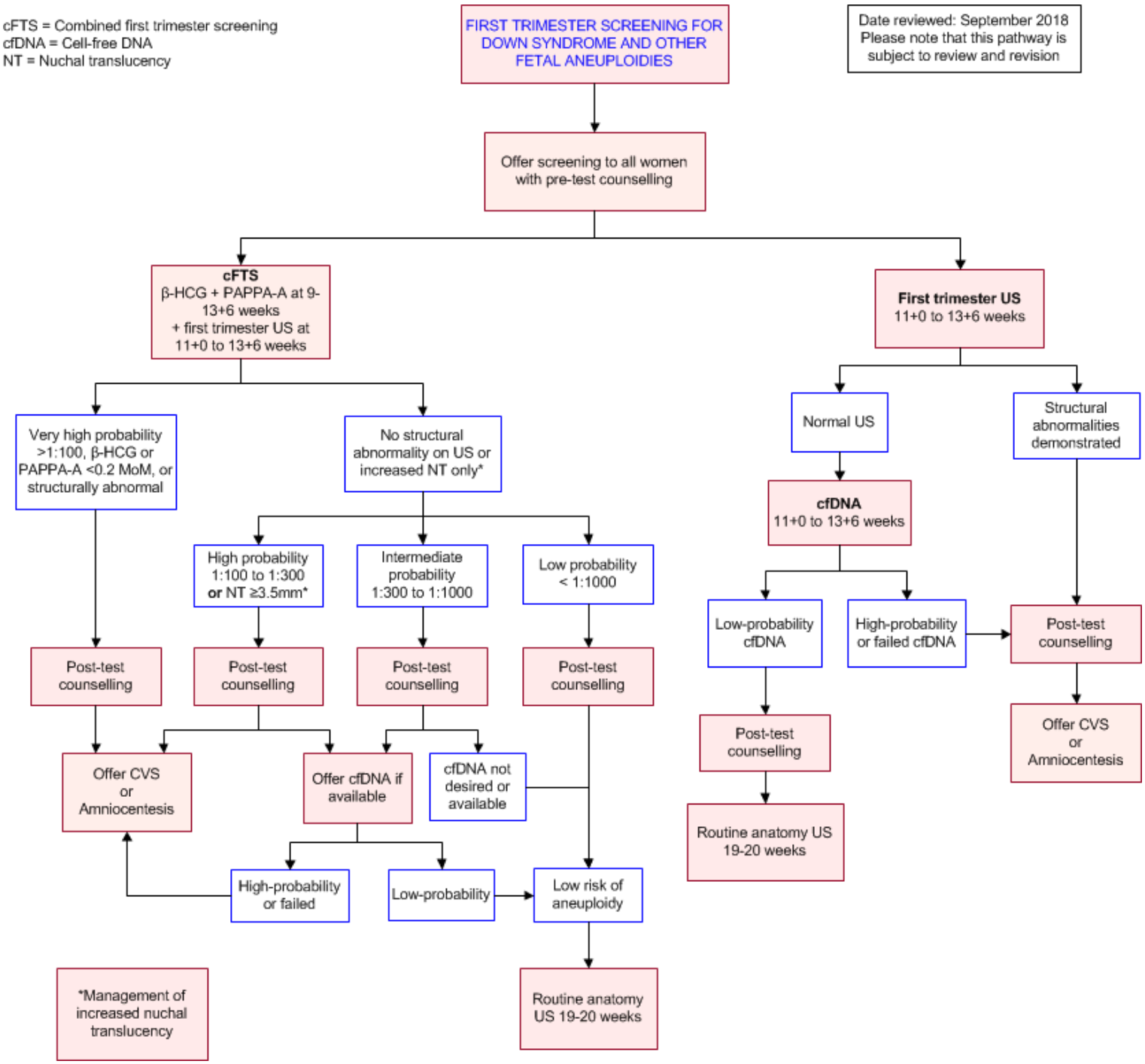

Image Gallery

*Note: *** Images coming soon ****

Teaching Points

- There are two screening tests available for the antenatal detection of Down Syndrome and other fetal aneuploidies: the combined first trimester screen and non-invasive prenatal testing (NIPT) with

cell-free DNA (cfDNA)
- Combined first trimester screening identifies 86-93% of Down Syndrome cases at a false positive rate of 3-5% in studies using a risk cut-off of 1:300. The components of the test include:
    - Age and past obstetric history
    - Serum ?-hCG and PAPP-A
    - Fetal ultrasound scan with measurement of nuchal translucency thickness
- If the calculated risk is higher than 1:300 then further testing is recommended, either with secondary screening with cfDNA if available, or with invasive diagnostic testing (chorionic villus sampling or amniocentesis)
- NIPT is a maternal blood test that detects chromosomal abnormalities using cell-free fetal DNA in the maternal circulation. cfDNA has demonstrated high accuracy in the detection of common fetal autosomal trisomies (T21, T18 and T13) and has been clinically validated in both high-risk and general obstetric populations with a sensitivity >99% and false positive rate ?0.1%
    - If undertaken as an initial screening test, measurement of NT is not necessary with cfDNA but an ultrasound examination should be undertaken prior to confirm viability, gestational number and to assess for significant structural abnormalities
- cfDNA is not a diagnostic test, so a high-probability result requires confirmation with chorionic villus sampling or amniocentesis
- Increased NT thickness and low PAPP-A are risk factors for fetal structural anomalies, so further investigation may be warranted even in normal karyotype fetuses

Pre- and Post-test Counselling

- Counselling of patients for first trimester screening is usually performed by trained general practitioners, radiologists, obstetricians or clinical geneticists
- The objective of counselling is to inform patients about the benefits, risks and implications of screening to allow them to consent to the tests, understand the results and be suitably knowledgeable to make further decisions based on the results. All testing should be undertaken voluntarily 1
- The primary aim of screening is to identify women at increased risk of having babies with trisomy 21 (Down syndrome), trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) and who may therefore benefit from further testing. Down syndrome is the most common and clinically significant aneuploidy. However, the process of scanning the fetus may, in some circumstances, reveal other morphological abnormalities such as a cystic hygroma (suggestive of Turner Syndrome), anencephaly, anterior abdominal wall and limb defects and other abnormalities which may or may not be related to other chromosomal abnormalities
- There are two available initial screening tests:
    - Combined first trimester screen
    - Cell-free DNA (cfDNA)
- Screening may involve combined first trimester screening only, cfDNA only or combined screening with cfDNA as a secondary screening test contingent on the result. 1-3 There are advantages and disadvantages to each screening strategy

Combined First Trimester Screening

- The combined first trimester screen calculates an adjusted risk for trisomies 21, 18 and 13 based on:
    - Age and past obstetric history

    - Maternal serum ?-hCG and PAPP-A
    - Fetal ultrasound scan with measurement of nuchal translucency thickness
- The blood test is optimal when taken from 9-13+6 weeks, and the ultrasound should be undertaken at 11 – 13+6 weeks gestation with chorionic villous sampling (CVS) available 4-6
    - Test timing is optimal for PAPP-A at 9-10 weeks and ?-hCG and ultrasound at 12 weeks 7
- The combination of fetal NT, maternal serum PAPP-A, ?-hCG and maternal risk factors identifies 86-93% of Down Syndrome cases at a false positive rate of 3-5% in studies using a risk cut-off of 1:300 7-14
- Women with a risk between 1:100 and 1:300 are further counselled on additional testing with chorionic villus sampling (CVS), amniocentesis or cell-free DNA (cfDNA) if available. There are advantages and disadvantages to each diagnostic strategy
- Current expert opinion suggests that cfDNA should not replace invasive diagnostic testing in women with very high risk (>1:10) after combined screening, 2 although there are no trials specifically assessing the ideal cut-off. Australian guidelines recommend invasive testing in women with cFTS risk >1:100, as there is an 18% chance of any major chromosomal abnormality, including a 3% risk of an abnormality not detectable on cfDNA testing 1,15
- Diagnostic testing is also recommended if any significant structural abnormality is detected 1,3
- Women with intermediate risk between 1:300 and 1:1000 may be offered cfDNA as a secondary screening test, or no further testing
    - cfDNA is a more sensitive test than combined screening so may provide further reassurance
- Any woman who is not sufficiently reassured by her aneuploidy probability from prior cFTS can be offered either follow-up screening with cfDNA or invasive tesing, considering the advantages and disadvantages of each 3
- Current guidelines recommend further testing in increased NT thickness ?3.5mm, regardless of cFTS result 3
    - cfDNA may be reassuring in a slightly increased NT, however diagnostic testing is more appropriate if NT is grossly abnormal. Read more about the management of increased nuchal translucency thickness
- Diagnostic testing is also recommended if PAPP-A or ?-hCG are less than 0.2 multiples of the median (MoM) as there is a 5% chance of an atypical chromosomal abnormality not detectable on cfDNA 3,15

Cell-free DNA

- Recently, screening with cfDNA in the maternal circulation has demonstrated high accuracy in the detection of common fetal autosomal trisomies (T21, T18 and T13) and has been clinically validated in both high-risk and general obstetric populations with a sensitivity >99% and false positive rate ?0.1% 16-22
- Diagnostic testing with chorionic villus sampling (CVS), amniocentesis is required to confirm a high-probability cfDNA result before deciding how to manage the pregnancy, as there is a significant false positive rate
    - The chance of an affected fetus after a high-probability cfDNA ranges from 46% to 90%, 20 compared to cFTS where the approximately only 20% of women with a high-risk cFTS will have fetal aneuploidy confirmed 15
- cfDNA may be offered to women as an initial screening test or as a secondary screening test contingent on the combined first trimester screen result
    - Australian guidelines recommend that cfDNA should not replace invasive diagnostic testing in women with very high risk cFTS (>1:100, as there is an 18% chance of any major chromosomal abnormality, including a 3% risk of an abnormality not detectable on cfDNA

testing) 1,15
    - cfDNA may be offered to women with a high risk combined screening result 1:100 to 1:300 or with an intermediate risk 1:300 to 1:1000
    - The optimum thresholds for high and intermediate risk groups may vary according to local factors 2,23
- cfDNA does not replace first trimester ultrasound. 2 Women electing to undergo cfDNA as a first-line screening test should undergo a first trimester ultrasound scan to confirm gestational age, number and that there are no major structural abnormalities that would warrant diagnostic testing
    - Subsequently detected significant structural abnormalities warrant invasive diagnostic testing even if cfDNA has been low-probability 2,3
- Women with a high-probability cfDNA result should be counselled for invasive diagnostic testing
- There is a higher rate of aneuploidy in women with failed tests, so proceeding to invasive diagnostic testing is recommended 3, 24,25
- The main advantage of cfDNA is that invasive testing and its associated risks may be avoided. Current literature suggests that cfDNA decreases the number of invasive procedures without reducing the detection rate of aneuploidies when used as a second-line test, 26-28 however a recent study did not find any reduction in the rate of miscarriage 29
- There is less information on the use cfDNA in twin pregnancies, however evidence that suggests that screening for T21 with cfDNA is feasible. 21,30-33 Unlike cFTS, cfDNA does not determine individual probabilities for each fetus 3
- The main limitations of cfDNA are the high cost to the patient and the time delay to results (and further diagnostic testing if needed), which could affect decision-making about continuing the pregnancy. The cost and time to result are both continuing to decrease as cfDNA becomes more widely available

Ultrasound

- Regardless of whether women elect for combined first trimester screening or cfDNA, the purpose of the first trimester ultrasound is to:
    - Determine fetal viability
    - Detect multiple pregnancies
    - Date the pregnancy
    - Identify major anatomical defects

Screening for aneuploidy

- If combined first trimester screening is undertaken, measurement of nuchal translucency (NT) is required for risk calculation
    - Nuchal translucency is the normal clear area in the fetal neck that lies between the skin and the soft tissues overlying the cervical spine, on a sagittal section through the fetus
    - The first trimester screening ultrasound should be performed between 11 weeks and 13 weeks 6 days gestation when crown-rump length (45-84mm) is optimal and timely diagnostic testing with chorionic villous sampling (CVS) is available. 4-6 It can only be performed with the appropriate software endorsed by the Fetal Medicine Foundation by trained ultrasound operators to achieve uniform results
- Increasing NT thickness is associated with an increasing rate of chromosomal defects and structural abnormalities. 6,34,35 A value ? 95th percentile (~2.1-2.7mm depending on gestational age) is generally considered abnormal, but adverse outcomes increase exponentially after ?3.5mm, equating to the 99th percentile
- Currently the significance of increased NT in women who have had low-probability cfDNA is uncertain. 2,36 An ultrasound examination is recommended prior to cfDNA in the first trimester. 2 This allows for detection of structural abnormalities that may warrant diagnostic testing 3

- Soft markers for T21 should not be assessed in women with low-probability cfDNA 2,3

Detecting other abnormalities or adverse perinatal outcomes

- Increased NT thickness is also associated with structural abnormalities and adverse outcomes in karyotypically normal fetuses, especially cardiac malformations. 37-41 Patients with NT measures of ?3.5mm, equating to ?99th percentile or ?2.5 MoM for gestational age, 42 should be referred for specialist, targeted early ultrasound at 16 weeks, fetal echocardiography, or both, even if the karyotype is normal or cfDNA is low-probability 43
- First trimester ductus venosus screening for congenital heart disease is only 83% and 80% sensitive and specific in patients with increased NT, and 15% and 96% specific in patients with normal NT 44
- A routine mid-trimester ultrasound has been shown to improve the prenatal detection of major fetal abnormalities. 45 Ultrasound examination is recommended between 18-22 weeks as visualisation of fetal structural anomalies is optimised at this time 46,47
- Assessment of neural tube defects (eg, spina bifida) is usually performed during the 19 week fetal morphology ultrasound scan and this cannot be easily detected in the first trimester screen

Chorionic Villus Sampling and Amniocentesis

- Chorionic villus sampling (CVS) and amniocentesis are invasive diagnostic tests for chromosomal abnormalities
- Both are performed under ultrasound guidance and may be performed by a trained radiologist or obstetrician
- Invasive tests are associated with risks, most notably the risk of pregnancy loss, however current risks are likely much lower than previously quoted

Chorionic Villus Sampling (CVS)

- Can be performed earlier than amniocentesis; CVS may be perfomed in the first trimester from 11 weeks 23
- Chorionic villi are collected for genetic evaluation without entering the amniotic sac, by a transabdominal or transvaginal approach 48
- Advantage: earlier prenatal diagnosis may give the option for an earlier (and therefore safer) termination if desired 48
- Disadvantage: 1-2% results may be false positives due to confined placental mosaicism 49
- Recent studies report the procedure-related risk of fetal loss as approximately 1 in 287 or lower 50-52

Amniocentesis

- May be perfomed in the second trimester from 15 weeks 23
- A sterile needle is introduced into the amniotic sac under ultrasound guidance and amniotic fluid is obtained and sent for testing 48
- Risk of pregnancy loss previously reported as lower than CVS, but recent studies have reported similar risk estimates 50-52

Nuchal Translucency

- Nuchal translucency is the normal clear area in the fetal neck that lies between the skin and the soft tissues overlying the cervical spine, on a sagittal section through the fetus

- Increasing NT thickness is associated with an increasing rate of chromosomal defects and structural abnormalities. 6,34,35 A value ? 95th percentile (~2.1-2.7mm depending on gestational age) is generally considered abnormal, but adverse outcomes increase exponentially after ?3.5mm, equating to the 99th percentile
- Current guidelines recommend further testing for NT ?3.5mm regardless of cFTS result 3
    - cfDNA and invasive testing are both options to investigate increased NT, however invasive testing is generally more appropriate if NT is grossly abnormal. Pregnancies with increased NT should be referred and the decision for further testing usually requires specialist input
    - It is important to note that 86% of chromosomally normal pregnancies with NT

Information for Consumers

Information from this website	Information from the Royal Australian and New Zealand College of Radiologists' website
Consent to Procedure or Treatment Radiation Risks of X-rays and Scans Ultrasound	Radiation Risk of Medical Imaging During Pregnancy Radiation Risk of Medical Imaging for Adults and Children Ultrasound 18-20 Week Screening Pregnancy Ultrasound Transvaginal Ultrasound

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